organisation of the collagen network within the cartilage. We are thus preparing methods to image this signal *in vivo* using FFC MRI and zero echo time acquisition techniques. We hope applications of this technique will allow new ways to non-invasively detect and stage osteoarthritic cartilage before morphological structural changes occur, as are appreciated with conventional MRI techniques.

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RELEASED MACROPHAGE MARKERS AS PREDICTORS OF KNEE OA PROGRESSION

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Purpose: Despite being one of the most common types of arthritis and a leading cause of disability worldwide, Osteoarthritis (OA) often goes undiagnosed until its later stages and little beyond palliative therapy is available. Biomarkers are particularly needed that can be used for prognosis or to monitor the efficacy of future therapeutics. There are many unanswered questions regarding the complex nature of joint tissue biology, but the role of innate immunity in the pathology of OA has become more evident in recent years. Specifically, synovial macrophage-produced cytokines drive aggrecanases, matrix metalloproteinases, and other destructive responses towards cartilage degradation. Moreover, the pattern of synovial fluid (SF) cytokines in knee OA is indicative of macrophage-mediated inflammasome activation. In a recent study, we showed that the quantity of folate receptor (FR-β+) macrophages in joints based on etarfolatide imaging correlated with radiographic knee OA. We also showed that sCD163 and sCD14, which are macrophage markers, correlated with inflammatory phenotypes and radiographic severity of OA. The goal of this study was to evaluate the effectiveness of using the macrophage marker, sCD163, as a prognostic tool for knee OA.
Methods: sCD163 was measured by ELISA in the synovial fluid of 86 subjects (128 knees) with knee OA from the Prediction of Osteoarthritis Progression (POP) cohort. The POP cohort provided baseline SF and serum samples and 3-year longitudinal follow-up to assess the predictive capability of sCD163 for radiographic OA structural progression based on either osteophyte formation or joint space narrowing. Models, using generalized estimating equations (to account for correlation within knees), were fitted with adjustment for age, gender, and body mass index (BMI), to evaluate associations of sCD163 with OA progression phenotypes. P values $\leq$0.05 were considered significant.
Results: Baseline synovial fluid sCD163 was associated with progression of knee OA; specifically SF sCD163 was associated with change in osteophyte severity ($p = 0.0107$), but not change in joint space narrowing. However, systemic sCD163 did not show any correlation with OA progression.
Conclusions: Shedding of CD163 from macrophages typically occurs in response to oxidative stress mediators and other inflammatory stimuli. The association of SF sCD163 with knee OA progression supports the growing inference that inflammation plays an important role in the progression of disease; this marker could prove useful for identifying a high-risk subgroup of knee OA patients. Furthermore, these results contribute to a growing literature identifying macrophages and macrophage-activation pathways as potential targets for new OA therapies.

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DETECTING KNEE CARTILAGE THICKNESS CHANGE AT THREE AND SIX MONTHS

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Purpose: Previous work found large differences (> 10%/y and < -10%/y) in knee cartilage thickness in distinct subregions of the joint between annual visits and these were more frequent in osteoarthritis patients than in asymptomatic subjects. Given these large observed changes in as little as 12 months, it is likely that important changes in cartilage thickness may be detectable at even shorter intervals. The goal of this study is to explore the magnitude of femorotibial cartilage thickness changes in participants with radiographic osteoarthritis (ROA) and asymptomatic subjects over three and six month observation periods. Data are available at 12 and 24 month periods for the same subjects and make it possible, for the first time, to directly compare short, i.e., 3 month, versus long-term, i.e., 24 month, changes. We also present robustness studies to assess the potential impact of observed, but statistically insignificant, differences between ROA and asymptomatic knees in the measurement error of cartilage thickness change.
Methods: Coronal MR images (3 Tesla) were acquired in 145 women (71 with ROA, 74 without symptoms or ROA) at baseline, 3, 6, 12 and 24 months. Femorotibial cartilage thickness was determined for five tibial and three femoral subregions in each (medial/lateral) compartment at each visit. Rapid change in knee cartilage in individual regions was classified via false discovery methods and the frequencies of rapid change were compared between ROA and asymptomatic subjects. Ordered values of knee regional cartilage thickness change in ROA and asymptomatic cohorts were also compared. Differences between ROA and asymptomatic subjects in measurement error, as estimated from scan/rescan analyses, were not statistically significant, but standard deviations were slightly higher (average of 10%) in ROA subjects. To assess possible differences in variability between the ROA and asymptomatic knees, thickness change in asymptomatic subjects were normalized by a) increasing change values by up to 60% across all regions; or b) increasing change values by up to 60% in central and external regions, while increasing change values in remaining regions by 5%.
Results: Rapid cartilage thinning was found in 18.3% of ROA subjects at Month 3 and this increased steadily over time with 25.4%, 33.8%, and 40.8% at Months 6, 12, and 24. These frequencies were higher (p-value < 0.05) than observed in the asymptomatic cohort at all visits except Month 3. In contrast, The percentage of subjects in the ROA cohort with rapid cartilage thickening was also statistically larger than frequencies observed in the asymptomatic cohort, but were 28.2%, 21.1% and 33.8% for Months 3, 6, and 12 and dropped to only 7% at Month 24 showing no apparent trend over time. Even after inflating asymptomatic change by 15 to 45% the frequency of rapid progression was still significantly higher in ROA cohort than in asymptomatic cohort, except at Month 3; see figure. While the largest percentage of subjects with rapid progression (thinning or thickening) at a given visit was 59%, overall the percentage of subjects with rapid progression at some visit was 81.7%. Also, although less than 8% of regions were classified as having rapid progression they accounted for 34% (at Month 3) to 64% (at Month 24) of observed variation from zero in thickness change. Results from ordered values were similar, but not as robust to adjusting standard deviation.
Conclusions: Regions with rapid subregional (focal) progression are an important component of cartilage thickness change in subjects with osteoarthritis. This study reaffirms the method used for classification is reasonable for estimating rapid progression in an ROA cohort. The results show that rapid thinning and thickening is detectable at six months and may also be present at three months.

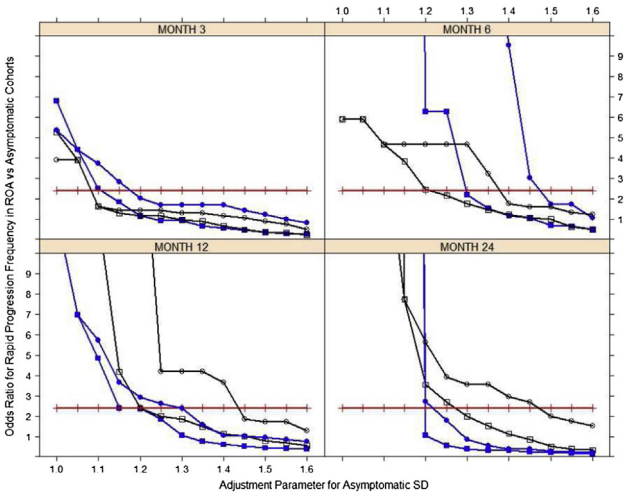

Figure 1. Odds ratio for Rapid Progression in ROA versus Asymptomatic Cohorts after various adjustments to underlying variability in Asymptomatic cohort.Black (open) = Thinning, Blue (closed) = Thickening, Red (dashes) represents $p = 0.05$ (approximately). square = SD adjustment equal for all regions, circle = adjustments differ between central and external regions and remaining regions.